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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,785	11/13/2003	Donald M. Coen	10498-00059	7812

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EXAMINER	
BULL, CHRISTOPHER	

ART UNIT	PAPER NUMBER
1655	

DATE MAILED: 10/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/712,785	COEN ET AL.	
	Examiner	Art Unit	
	Christopher Bull	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1006*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention."
> *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials."
> *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973)
> ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...")
> *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art*, (2) *partial structure*, (3) *physical and/or chemical properties*, (4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function*, and the (5) *method of making the claimed invention.*

In the instant case, the independent claims 1 and 8 are drawn to fluorescence polarization methods of testing compounds for inhibiting binding between fragments of two proteins which mutually associate. Independent claim 14 is similar, but the two fragments are derived from the known two subunits of Herpes Simplex Virus (HSV): the labeled smaller being "substantially homologous to an 18 amino acid C-terminal fragment of catalytic subunit", and the unlabeled larger being "a functional fragment of the processivity subunit". Claims wherein neither of the proteins from which the

fragments are to be made have been defined therefore cover a huge number of mutually associating proteins, completely unrelated to HSV polymerase. Claims with only one of the two proteins defined would still include antibodies to HSV polymerase, and the added variable of fragmentation effectively makes the possibilities infinite. Even in claim 18 where both proteins are defined, the number of possible fragments in the claimed genus is still very large, as explained further below.

(1) Level of skill and knowledge in the art:

The level of knowledge in the art of protein synthesizing and sequencing is high, but that of predicting the functional consequences of any given fragmentation, alteration, insertion and/or deletion of a protein sequence is not.

(2) Partial structure:

Even if one or the other fragment were composed of SEQ ID #1 or SEQ ID #2, the number of possible mutually associating fragments for the other protein as claimed is still staggering. If both are defined as in claims 11 and 18, there are still a very large number of possible fragments to consider. For example, "comprising a peptide which is substantially homologous to an 18 amino acid..." may include deletions, with or without additional residues at the ends and/or unrelated insertions within the sequence. Similarly, a peptide in which a "functional fragment of the processivity subunit comprises a protein including SEQ ID #2" has even more possible variation, since the sequence is much longer and the requirements for functionality relatively unknown.

(3) Physical and/or chemical properties:

The disclosure gives no physical or chemical properties for the range of compounds claimed, nor even properties for the two fragments tested.

(4) Functional characteristics:

The minimum sequence requirements of a fragment from the processivity subunit which retains "function" are not defined in the disclosure. The disclosure also does not contain any minimum level of the various possible activities that would still be considered functional.

(5) Method of making the claimed invention:

The disclosure teaches only preparations for the two fragments actually tested, and the actual testing was confined to only that pair of fragments.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claims 1, 14, and 18 are broadly generic, with respect to all possible compounds encompassed by the claims. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification.

Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives. While having written description of the two fragments tested, and compounds identified in the specification tables and/or examples, the specification is void of any other peptides with functional characteristics that qualify.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "substantially homologous" and "functional fragment" in claims 14-18 are relative terms which renders the claim indefinite. The term "substantially homologous ", while defined variously in the Specification as 90, 95 or 99% homology, is not defined as to any required length of peptide either by the claim or specification, or whether deletions and/or insertions are contemplated. The specification does not provide a standard for ascertaining the requisite length, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Similarly, the term "functional fragment" contains no metes or bounds on what level of activity would be considered functional.

The Disclosure, on page 17 line 15, defines functional as "retaining substantially all native functions", but without making definite which activities or what is meant by "substantially" in this case. Indeed, the phrase (page 17, lines 14-15) "... a truncated version of UL42 ... retained all known biochemical activities of UL42 ... but unlike full-length UL42." Seems to suggest there may indeed be some differences in activity.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 6-8, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Lynch et al. (US 6,207,397 issued March 2001).

Lynch et al. teach methods of identifying inhibitors of protein:protein interaction using fluorescence polarization, wherein '...the term protein:protein interaction, and the terms "protein", "peptide" and "polypeptide" are used interchangeably.', see, e.g., Col 4, lines 43-45 and Col 34, Claim 11:

"An in vitro assay method for identifying a test substance which inhibits the mutual association of two protein molecules, said method comprising:
a) providing a first protein molecule and a second protein molecule capable of mutual association, said second protein molecule bearing a covalently linked fluorophore,
(b) preparing a mixture containing said first and second protein molecules and at least one test substance,
(c) irradiating said mixture with polarized light of a suitable wavelength permitting excitation of the fluorophore as indicated by emission of polarized light,
(d) measuring the degree of polarization of the emission, and
(e) determining the effect of the presence or concentration of the test substance in decreasing the observed emission polarization of a mixture of the first and second protein molecules in the absence of said test substance."

Please note that Claims 1 and 8 as instantly claimed read upon Claim 11 of Lynch et al. (wherein the arbitrary definition of the first protein as smaller and labeled vs. the second as larger and unlabeled are reversed). Lynch et al. also contemplate (Col. 7, lines 36-47) use with combinatorial libraries and multiple compounds per assay. Therefore, the reference is deemed to anticipate the above claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6-11, and 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keating et al. (June 2000) in view of Zuccola et al. (Feb., 2000).

Keating et al. teach the use of fluorescence polarization for identifying inhibitors of mutual association in protein fragments capable thereof (entire paper, particularly Conclusions, page 136), in the same way as discussed above for Lynch et al. They further state that (end of Abstract) "These measurements aid in the iterative synthesis of more potent and selective compounds." Keating et al. show that equipment for polarization assays in multi-well plate format was commercially available at the time the

claimed invention was made (page 130). They recommend the technique as providing "a more uniform method for assessing and comparing agonist potencies for small molecule lead optimization.", all in the context of high-throughput screening of combinatorial libraries. Keating et al. did not examine binding inhibitors of the specific two protein subunits of Herpes Simplex Virus (HSV) DNA polymerase of the instant application, although they do state (end of page 128) that "Using this method the affinity of different receptor ligand interactions can be measured in a single assay configuration." Thus, employing conventional fluorescence polarization as an effective means to screen compounds for inhibition of a protein:protein mutual association was well known and accepted in the art.

Zuccola et al. (Feb., 2000) beneficially teach the crystal structure of the complex formed using two related fragments of HSV DNA polymerase: the C-terminal 36 residues (also called peptide A) of the HSV catalytic subunit (Pol); and the N-terminal 319 residues (SEQ ID #2) of the processivity subunit (the factor UL42). They review the activity measurements done on each of these two fragments, as well as the known activity of an 18-residue portion of peptide A that is SEQ ID #1 (page 268). They also stress the need and benefit to finding such inhibitors as novel drug candidates (page 268). Zuccola et al. did not use fluorescence polarization in their studies.

Claims 1-4, 5-11, and 13-18 are drawn to fluorescence polarization methods of finding inhibitors for the specific binding of fragments from the two HSV DNA polymerase subunits, including SEQ ID #1 & 2. In these claims, a fluorescent label is

attached to the smaller of the two fragments, as recommended by Keating et al., and test compounds used to inhibit the mutual association of two protein fragments.

The references are relied upon for the reasons set forth above. Based upon the overall teachings provided by the primary reference (as discussed *supra*), it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use fluorescence polarization to monitor the mutual association of these fragments of HSV DNA polymerase subunits via the instantly claimed steps, and to incorporate the choice of HSV protein fragments from the secondary reference therein. It would further have been obvious to one of ordinary skill in the art to include the shortened UL42 fragment of SEQ ID #1 and/or that of SEQ ID #2, based on the beneficial teachings of Zuccola et al. Note that Zuccola et al. expressly comment on the desirability of finding novel inhibitors of this interaction, providing motivation to do so. The adjustment of conventional working conditions [e.g., art-recognized buffers, temperatures, optimal wavelengths for fluorescence excitation and emission, etc.] is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

Therefore, these inventions as a whole were *prima facie* obvious to one of ordinary skill in the art at the time the inventions were made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1, 4-8, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lynch et al. (US 6,207,397 issued March 2001) in view of Gee et al. (US 6,162, 931 issued Dec. 2000).

Lynch et al. taught the use of fluorescence polarization for identifying inhibitors of mutual association in protein fragments capable of thereof (as discussed above), including labeling with the fluorophores then known. Lynch et al. did not teach the use in such an assay of Oregon Green, which was not yet available by their filing date.

Gee at al. beneficially teach the use of Oregon Green (2', 4, 5, 7, 7'-pentafluorofluorescein) derivatives to label proteins and peptides, as having photostability superior to fluorescein with the additional benefit in having lower sensitivity to pH changes in the physiological range of 6-8 than non-fluorinated fluorophores. Oregon Green also provides a better match to the 488 nm excitation line of an argon laser than does fluorescein. Derivatizing agents incorporating Oregon Green have been advertised commercially since 2000. Gee et al. specifically mention use of Oregon Green derivatives in the context of fluorescence polarization assays (Col 26, lines 27-28), providing motivation to apply the above benefits in such assays.

Based upon the overall teachings provided by the primary reference (as discussed *supra*), it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to incorporate the choice of the superior fluorophore from the secondary reference when using fluorescence polarization to monitor the mutual association of protein subunits via the instantly claimed steps.

Therefore, these inventions as a whole were *prima facie* obvious to one of ordinary skill in the art at the time the inventions were made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Bull whose telephone number is (571) 272-1327. The examiner can normally be reached on 7:30-4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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CHRISTOPHER R. TATE
PRIMARY EXAMINER